MEDICAL PROGRESS:

Histamine and the Antihistaminic Drugs

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SUMMARY

The tissues affected by histamine and anaphylactic reactions are identical. Epinephrine antagonizes the action of histamine by acting on effector cells in a direction opposite to that of histamine. The so-called antihistaminic drugs block rather than antagonize the action of histamine. The injection into the human body of epinephrine or certain antihistaminic substances provokes the release of histamine and thereby produces a rise in the histamine blood level.

There is a remarkable conformity of potency of antihistaminics as determined by Dale experiments and by histamine intoxication experiments in the intact guinea pig. Neoantergan, Pyribenzamine and Histadyl are usually superior to other compounds when potency is assayed by these methods.

All antihistaminics provide similar protection again animal anaphylaxis. Larger doses are necessary to protect against anaphylaxis than against histamine intoxication.

The differences in potency as determined by Dale experiments and histamine experiments in animals are not found in clinical use. One compound is not generally superior to all others in the treatment of any one or several allergic disorders.

The antihistaminic drugs are beneficial in the symptomatic treatment of allergic rhinitis, acute urticaria and angioneurotic edema, and mild non-infective bronchial asthma. Their effectiveness in the management of moderately severe and severe non-infective bronchial bronchial asthma; infective bronchial asthma; migraine; atopic dermatitis (disseminated neurodermatitis), and pruritus of skin disorders other than acute urticaria and angioneurotic edema, is not worthy of particular commendation.

The size of the dose of any antihistaminic substance influences the incidence of but not the type of side-effect that may accompany its usage. The quality of side effects varies according to the drug, although there is an individuality of response for each patient which must be reckoned with. In selecting an antihistaminic compound it is necessary to consider the percentage of cases in which side-effects occur, as well as the percentage of good results. Optimal results are obtained by employing combinations of compounds and changing from one to the other as the case demands.

THE principal actions of histamine are: (1) to evoke contraction of the smooth muscle in the bronchioles, intestines and uterus; (2) to dilate arterioles and cause increased permeability of capillaries; and (3) to act as a secretogogue for the lacrimal, nasal, pulmonary and digestive glands of external secretion. The most prominent pharmacological effects of histamine, therefore, are due to its action upon involuntary muscle, upon vascular endothelium and upon the glands of external secretion.

In the anaphylactic body the only tissues which, according to present evidence, are directly responsive to the antigen-antibody reaction are involuntary muscle, capillary endothelium and possibly certain glandular cells. The tissues affected by histamine and anaphylactic reactions are identical and it has naturally been assumed that the tissue response from the antigen-antibody reaction is due to a release of histamine or a histamine-like substance.

Epinephrine favorably combats the anaphylactic reaction. Furthermore, epinephrine and histamine act on effector cells in opposite directions and the action of one tends to neutralize the action of the other. Epinephrine, therefore, is an effective antihistaminic substance and this type of antihistaminic action is spoken of by the pharmacologist as physiologic antagonism. This physiologic antagonism between epinephrine and histamine may be at play within the body constantly as a compensatory mechanism. To lend support to such a theory is the recent evidence that the intravenous administration of epinephrine or synephrine provokes a significant increase in the histamine blood level. The percentage of rise in the histamine blood level in allergic and normal individuals following the intravenous injection of 0.2 mg. of epinephrine is similar, although the (resulting) histamine blood level in allergic patients is frequently higher (160 ug. per cc.) than

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that found in normal controls (60 to 80 ug. per cc.).[85, 6, 79, 83]

An exemplification of the extent to which eccentricity may accompany scientific endeavors is the confusing evidence that there is an increase in the blood histamine level following an injection of either Antergan,® Neoantergan® or Phenergan.®[64] To explain this aberration from logical expectancy Pellerat[64] has conceived the theory that tissue histamine is displaced by antihistaminic substances and liberated into the blood. The acceptance of Pellerat's data must await confirmation by other investigators.

Another facet to the inspiring theory of the compensatory mechanism between histamine and epinephrine has lately been added. Fatal pulmonary edema in rabbits and guinea pigs following intravenous epinephrine can be prevented by pretreatment with antihistaminic substances. The explanation ventured is that pulmonary edema from epinephrine is the sequela of histamine release.[35, 69]

Recently[92] it has been proposed that "epinephrine-fastness" may be partially due to the release of histamine by epinephrine. In other words, the successive administration of epinephrine to an "epinephrine-refractory" asthmatic patient might act to aggravate the condition by releasing additional histamine.

It occurred to the author that the unfavorable reaction in the nasal mucous membranes of patients following the indiscriminate usage of vasoconstrictor drugs might be due to the local release of histamine. Could it be, therefore, that the deleterious local effects of epinephrine, Privine,® Neosynephrine® and ephedrine that are frequently observed in habitual users of these drugs are due to the liberation of histamine in the nose? And could such a reaction be prevented by adding antihistamine substances to vasoconstricting nasal solutions? In an attempt to answer these questions, nasal solutions containing (1) Privine 0.05 per cent and Pyribenzamine® 0.5 per cent and (2) Privine 0.05 per cent and Antistine® 0.5 per cent have been prepared by the Ciba Pharmaceutical Company. To date such solutions have been given to 100 patients with allergic rhinitis and although at this early date it is difficult and premature to judge their value, certain impressions have been acquired. The symptomatic relief obtained from both preparations has been spectacular; no unfavorable reactions from Privine have been encountered; and two patients who could not tolerate Privine alone have used both of the combined preparations with impunity. The complaint of burning in the nose that is known to follow at times the instillation of Pyribenzamine solution (0.5 per cent) has been observed to occur from the Privine-Pyribenzamine mixture. The Privine-Antistine solution, however, rarely causes burning. As to effectiveness the two mixtures are comparable.

Epinephrine and related vasoconstrictor drugs, therefore, inasmuch as they act in antagonism to histamine, are well defined as antihistaminics. However, may Benadryl,® Pyribenzamine,® Histadyl® properly be called antihistaminics? These so-called antihistaminics, by themselves, do not cause any significant degree of muscular relaxation nor do they have any direct effect upon the peripheral blood vessels. They are drugs that block, rather than antagonize histamine. In other words, the mechanism of action is similar to that by which atropine blocks the effects of acetylcholine. The term histaminolytic would be more applicable.[28] In this presentation, however, the term antihistaminic as it is commonly interpreted and defined in the medical literature will be employed.

Within the past three years the medical literature has been studded with reports on antihistaminic substances. Because of the great and unfortunate variety of techniques used in studying these compounds it has become increasingly difficult and hazardous to interpret, analyze, compare and evaluate the data submitted. Particularly treacherous is the evaluation of clinical observations where the personality equations of the investigator and the patient are so variable. Then, too, the very nature of the allergic condition makes for difficulty in the appraisal of any therapeutic agent.

For the sake of clarity, accuracy and simplicity the data analyzed in this report will be presented under the following headings: (1) chemistry, (2) in vitro experiments, e.g., studies employing the Dale technique, (3) in vivo animal experiments concerned with activity against histamine intoxication and against anaphylaxis, (4) clinical observation, and (5) side effects.

CHEMISTRY

Upon scrutiny of the chemical structures of the multifarious antihistaminic substances, certain factors common to the most potent ones become apparent. Many can be segregated into two groups dependent upon the existence in the molecule of the basic unit, ethanolamine (Benadryl, Decapryn) Figure 1, or the basic unit ethylenediamine (Pyribenzamine, Histadyl, Neoantergan, Antergan, Bromothen, Chlorothen, Neohetramine) (Figure 2). Common to these two groups is a terminal N atom which is a tertiary amine and this component of the structure contributes favorably to the potency of the entire molecule.[30] Dimethyl amine instead of diethyl amine groupings on the tertiary amine make the compounds less toxic. The chain length between the O and the N or the N and the N atoms is not more than two C atoms. Increased length and branching detract from activity. Certain alterations of the aromatic nuclei attached to the alpha N atom can be made without interfering with activity. A displacement of the pyridyl (Pyribenzamine, Neoantergan, Histadyl, Bromothen, Chlorothen) with the pyrimidyl group (Hetramine, Neohetramine) does not interfere appreciably with potency. The addition of a para-methoxyl group to the benzol nucleus enhances activity (Neoantergan versus Antergan; Neohetramine versus Hetramine). Furthermore, the benzol group may be converted to a thenyl (Histadyl or Thenylene) or halogenated thenyl group (Bromo-

then, Chlorothen) without impairing effectiveness.[48, 51]

The structural formulae of Trimetron, Antistine, Phenergan and Thephorin (Figure 3) vary in different degrees from the two large groups of compounds already discussed. There is great similarity in structure between Trimeton and Pyribenzamine and Benadryl but in the former substance a methane grouping has been substituted for the O atom of Benadryl and the alpha N atom of Pyribenzamine. In Antistine the terminal N atom has become a part of a heterocyclic compound. Phenergan has a phenothiozine molecule and an isopropyl group connecting the two N atoms. Thephorin is completely unlike any of the compounds. All of these antihistaminics, regardless of structure, possess clinical activity of a comparable degree, as will be pointed out later in this discussion.

IN VITRO EXPERIMENTS

Dale experiments. Ineluctable deceptions and unavoidable inaccuracies accrue from experiments with the Dale technique because of the erratic behavior of the isolated intestine.[16, 45] Because of this and the slight variations in technique employed by different investigators, precautions and heedfulness must be exercised in evaluating small differences in effectiveness of compounds tested.

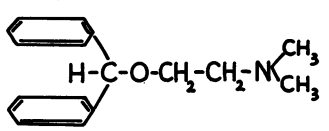
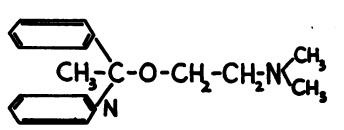
By exercising conservatism, certain conclusions can be drawn, even despite the hazards offered by this technique. Histadyl,[45, 48] Chlorothen,[45, 51] Bromothen,[45, 51] Pyribenzamine[45] and Neoantergan[45, 75, 90] are more potent than Phenergan[45, 31] and Benadryl;[45, 75, 29] and Antistine[45, 29] is the least potent of all.

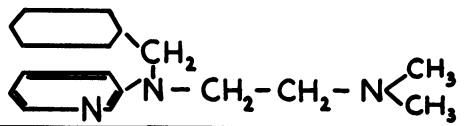
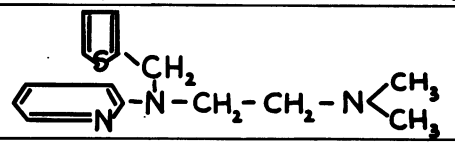
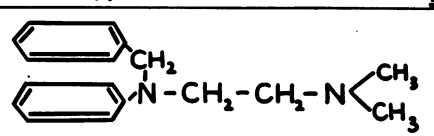
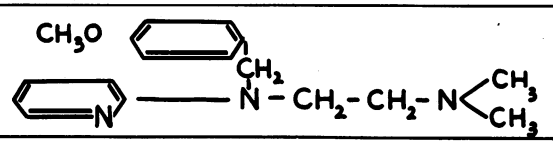
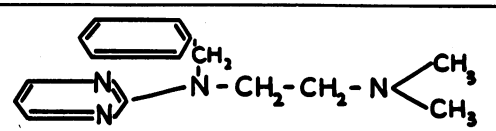
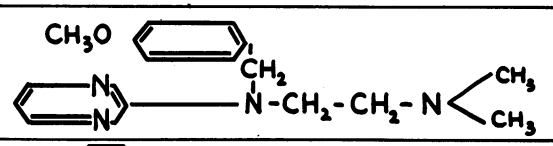
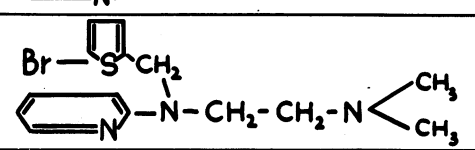
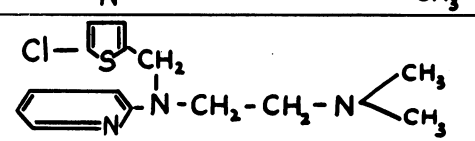
IN VIVO EXPERIMENTS

Histamine intoxication. Three methods have been used to study the blocking effect of antihistaminics in the intact guinea pig: (1) the injection of a fixed dose of antihistamine substance prior to the intravenous administration of histamine in order to ascertain the number of lethal doses of histamine that can be tolerated,[32, 33] (2) the administration of antihistaminics by injection or by mouth and noting the protection against histamine aerosol,[90, 33, 55] and (3) the determination of the smallest amount of antihistamine substances that will afford protection against one lethal dose of histamine injected intravenously,[90] intracardially[46] or intraperitoneally.[71, 21]

Slight differences in the comparative effectiveness of the various antihistaminics, due to the diversity of methods and procedures, are insignificant. However, it is noteworthy that whenever Neoantergan has been compared with other antihistaminics, regardless of technique employed for testing, it has

COMPOUNDS WITH Ethanolamine AS A BASIC UNIT

COMMON NAME	CHEMICAL NAME	FORMULA
Benadryl	β-dimethylaminoethyl benzhydryl ether.	
Decapryn	Dimethylaminoethoxy-methylbenzylpyridine.	

COMPOUNDS WITH Ethylenediamine AS A BASIC UNIT		
COMMON NAME	CHEMICAL NAME	FORMULA
Pyribenzamine	N'-pyridyl-N'-benzyl-N-dimethylethylenediamine.	
Histadyl or Thenylene	N'-pyridyl-N'-thenyl-N-dimethylethylenediamine.	
Antergan	N'-phenyl-N'-benzyl-N-dimethylethylenediamine.	
Neoantergan	N'-*p*-methoxybenzyl-N'-pyridyl-N-dimethylethylenediamine.	
Hetramine	N'-benzyl-N'-2-pyrimidyl-N-dimethylethylenediamine.	
Neohetramine	N'-*p*-methoxylbenzyl-N'-2-pyrimidyl-N-dimethylethylenediamine.	
Bromothen	N'-pyridyl-N'-5-bromothenyl-N-dimethylethylenediamine.	
Chlorothen	N'-pyridyl-N'-5-chlorothenyl-N-dimethylethylenediamine.	

always proven to be the most effective,[90, 29, 46] with Pyribenzamine,[51, 90, 46] Histadyl,[46, 21] Bromothen,[46] Chlorothen,[46] Benadryl,[90, 29, 46, 21] Phenergan,[46] Hetramine,[90] and Antistine[29, 46] usually rated in regard to comparative potency in the order enumerated.

There is, therefore, a remarkable conformity in regard to the order of potency of the various antihistaminic compounds as determined by the Dale technique and by the in vivo experiments in the intact guinea pig when testing for activity against histamine intoxication.

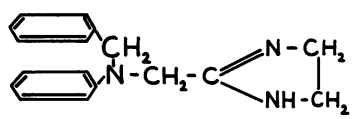
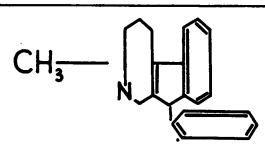
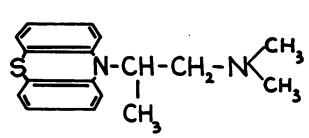
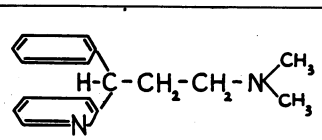
Animal anaphylaxis. Guinea pigs have been employed by most investigators for anaphylaxis experiments, and a great variety of foreign proteins have been used as sensitizing antigens. The usual procedure has been to administer the sensitizing dose of antigen; wait 14 to 21 days for hypersensitivity to develop; administer the antihistaminic substance, and then within 10 to 60 minutes thereafter give the challenging dose of antigen. By this method of investigation, Neoantergan,[46, 71] Antergan,[71] Pyribenzamine,[46, 71, 4, 54, 67] Histadyl,[46] Bromothen,[46] Chlorothen,[46] Thephorin,[49] Neohetramine,[67] Benadryl,[46, 71, 54, 76] Hetramine,[22] Phenergan[31, 46] and Antistine[46] have been shown to be potent. Very few investigators have studied the comparative effectiveness of many different compounds. However, Landau and co-workers,[46] studying nine compounds, found that the amounts of Neoantergan, Pyribenzamine, Histadyl, Bromothen, Chlorothen, Benadryl, 1721 (Searle), and Phenergan needed for protection were almost equal, and that larger doses of Antistine were required to similarly protect animals. Rose and co-workers[23] reported that Neoantergan, Pyribenzamine, Antergan and Benadryl were equivalent in protective power.

For protection against anaphylactic shock much higher doses of antihistaminics are required than for protection against histamine intoxication.[46] Because of this discrepancy it is not necessary to imply that anaphylaxis in the guinea pig is not the result of histamine release. It is probable that there is intracellular release of histamine as a result of antigen-antibody reaction.[28] Because of this, the opportunity for effectiveness of a blocking substance is less than it would be if the histamine came to the cells by way of the bloodstream. It is, therefore, intelligible why reactions to histamine which depend upon diffusion of histamine into tissues from the bloodstream can be more competently blocked by antihistaminics than can those reactions which result from release of histamine directly within the effector cells.

CLINICAL OBSERVATIONS

General. There are very few data available on the stability of antihistaminic substances. Trimeton discolors slowly on exposure to sunlight and reacts

MISCELLANEOUS COMPOUNDS

COMMON NAME	CHEMICAL NAME	FORMULA
Antistine	N'-phenyl-N'-benzyl aminomethylimidazoline.	
Thephorin	2-Methyl-9-phenyl-2 3,4,9-tetrahydro-1-pyridindene.	
Phenergan	N-dimethylamino-isopropylthiodiphenylamine.	
Trimeton	2-pyridyl B-N,N,-dimethylaminoethyl-methane.	

with rubber.[74] Landau and Gay[45] reported that Phenergan had oxidized en route from France to their laboratories and that the potency of high dilutions of several drugs decreased even though they were refrigerated. They did not enumerate the drugs so affected.

The dearth of data on absorption and excretion is regrettable. Following the administration of 400 mg. of Benadryl in 50 cc. of water by mouth under fasting conditions, the concentration of Benadryl in the blood reaches a peak of 1.07 ug. per cc. within a period of 90 to 120 minutes. Under similar circumstances Pyribenzamine attains a peak of concentration of only 0.4 ug. per cc. after 180 minutes. Twenty-four hours after 400 mg. of Benadryl and Pyribenzamine were administered orally, 46 per cent and 20 per cent, respectively, were excreted in the urine.[56]

Benadryl administered orally in therapeutic doses has no effect on the body temperature, the basal metabolic rate, the body weight, the pulse rate, the blood cell structure, the electrocardiogram, or the glucose tolerance curves.[57, 58, 68] There may be a decrease in the blood pressure which persists for one to two hours following the oral administration of 50 to 100 mg.[23] However, following the intravenous administration of 200 mg. and 300 mg. of Benadryl in 50 cc. of distilled water the systolic and diastolic blood pressure rises an average of 30 to 40 mm. and 20 to 30 mm. respectively. The pulse rate also increases 20 to 25 beats per minute. This cardiovascular reaction persists for about 60 minutes and then begins to subside.[53]

Pyribenzamine given orally in doses of 150 mg. a day has no effect on body weight, blood pressure, urine, urea blood nitrogen, liver function or blood cells.[44]

Neohetramine[17] in daily doses of 200 to 400 mg. and Thephorin[18] in a daily dose of 300 mg. by mouth do not affect blood cells, urine, blood pressure or electrocardiogram of normal individuals. Inversion of the T waves in Lead C V_4 in patients with arteriosclerotic heart disease has been observed following the oral administration of 300 mg. of Thephorin. The changes disappeared after withdrawal of the drug.[18]

Electroencephalograms following the administration of 200 mg. doses of either Benadryl, Pyribenzamine, Neohetramine or Thephorin show identical changes of fast activity superimposed on a normal alpha rhythm. There may also be a decrease in the amplitude of the waves.[18]

Seasonal and perennial allergic rhinitis. The therapeutic effectiveness of antihistaminic drugs is not modified by the type of antigen setting off the hypersensitive reaction in the nose. The symptoms of sneezing, rhinorrhea, lacrimation, and itching of the eyes and nose are better relieved than is nasal congestion.[27] Pyribenzamine,[27, 8, 37, 52, 2, 89] Hydryllin,[27, 2] Antistine,[27, 2, 24, 88] Neoantergan,[27, 8, 2, 89, 88, 78] Histadyl,[21, 27, 63, 25] Benadryl,[27, 8, 52, 9] Thephorin,[18, 70] Neohetramine,[17, 2, 88, 7] Chlorothen,[27] Decapryn,[14, 76] and Trimeton[88, 13, 91] give beneficial results in from 60 to 80 per cent of the patients treated. The degree of relief depends upon the dosage employed and the patient's tolerance of the drug. Although Pyribenzamine, when it has been compared with other substances, has proved to be superior in effectiveness,[27, 8, 37, 2] this difference is not great and it is imperative to stress that any one compound is not generally superior to all others. It is not an uncommon experience to find patients that will benefit from one drug but not another, so that if symptomatic relief is not forthcoming during treatment with a particular antihistaminic substance, other compounds should be given a trial.

The oral dose for all compounds is similar. At the onset of treatment a small dose (25 to 50 mg.) administered regularly after each meal and at bedtime, or periodically as necessary to relieve symptoms, is advisable. The dose may be increased until relief is obtained or until side-effects are experienced. Larger amounts of Antistine[27] and Neohetramine[7] than of other antihistaminics are necessary to provide comparable relief.

The topical application of two to three drops of a 0.5 per cent solution of Pyribenzamine in the nose every three to four hours gives symptomatic relief and reduces the engorgement of the inferior turbinates. The duration of relief varies from one to 24 hours depending upon the severity of the symptoms. Local reactions such as burning in the nose and pharynx and sneezing occur, but general reactions have not been reported.[12] The topical application of one to two drops of a 0.5 per cent solution of Antistine in the eyes is usually non-irritating and often effective in the relief of the itching and the burning caused by the allergic reaction in the conjunctivae.[24]

The gratifying symptomatic relief afforded by the antihistaminic compounds must not diminish the search for etiological factors and must not encourage the withholding and exclusion of specific desensitization therapy. Desensitization with specific antigens as a therapeutic measure by itself is superior to symptomatic treatment with antihistaminic drugs. Furthermore, asthma is likely to develop in patients with allergic rhinitis during treatment with only antihistaminic substances, whereas, asthma rarely occurs in patients receiving perennial or preseasonal desensitization therapy. Desensitization and antihistaminic substances employed together provide the optimal opportunities for efficacious results.[89]

Bronchial asthma. Critical investigators have called attention to the poor results obtained in the treatment of bronchial asthma. About 25 to 50 per cent of the patients treated with Pyribenzamine,[27, 8, 37, 52, 2] Hydryllin,[27, 2] Antistine,[27, 24] Neoantergan,[27, 8, 2, 78] Histadyl,[27] Benadryl,[8, 52, 9] Thephorin,[18] Neohetramine,[17] Decapryn,[14, 76] and Trimeton[13, 91] are benefited. In a few instances where the effectiveness of several compounds has been compared, Hydryllin[27, 2] and Neoantergan[27] have met with the most success. But in the treatment of asthma as in the treatment of allergic rhinitis the

differences in effectiveness of the various drugs are not of sufficient degree to merit dogmatism. Only patients with non-infective bronchial asthma presenting very mild symptoms are benefited. Patients with infective bronchial asthma are not affected favorably and it is probably not wise to attempt treatment of such patients with the antihistaminic compounds because of the drying effect.

Urticaria and angioneurotic edema. The antihistaminic drugs attain their zenith of effectiveness in acute urticaria and angioneurotic edema. Pyribenzamine,[27, 8, 37, 52, 5, 42, 1] Antistine,[27, 24, 61] Benadryl,[8,52,9,5,42,1] Histadyl,[27,42] Neoantergan,[27,39] Hydryllin,[27] Neohetramine,[17, 7] Thephorin,[18] Decapryn[14] and Trimeton[13] are of comparable effectiveness. From 60 to 90 per cent of patients treated receive varying degrees of subjective and objective relief. Pruritus is usually the first clinical manifestation to be ameliorated, and alleviation of erythema and edema follows. Pruritus may be promptly abated by the intravenous administration of from 20 to 50 mg. of Benadryl in 75 to 100 cc. of isotonic sodium chloride solution and this mitigation usually persists four to eight hours.[9] The author has procured more satisfactory and durable palliation by administering 100 mg. of Benadryl in 250 cc. of isotonic sodium chloride solution over a period of one to three hours and repeating the procedure as necessary throughout a 24-hour period. Only Benadryl and Histadyl are commercially available in solutions for parenteral injection. Chronic urticaria and angioneurotic edema respond less dramatically to antihistamine therapy than the acute forms.

Pruritic dermatosis other than urticaria and angioneurotic edema. The antihistaminic drugs do not alter the course of any skin disease other than by the indirect effect of reducing trauma through the amelioration of pruritus. An appraisal of the efficacy of such drugs in the relief of pruritus is made particularly untrustworthy because of the subjective nature of the symptom. Baer and co-workers[5] studied the effect of oral Benadryl and Pyribenzamine on patients with atopic dermatitis (disseminated neurodermatitis), eczematous dermatitis, erythema multiforme, chronic discoid and lichenoid dermatosis, acne vulgaris, psoriasis, lichen planus, pruritus vulvae and ani, generalized pruritus, lichen chronicus simplex and dermatitis medicamentosa. They concluded that only 10 per cent of their patients experienced commendable easement of itching. Other investigators employing Pyribenzamine,[8, 52] Benadryl,[8, 52] Neohetramine,[17] Thephorin,[18] and Trimeton[13] orally in the treatment of atopic dermatitis and contact dermatitis have reported disappointing results. The patch test reaction to poison ivy extract cannot be lessened by administering Pyribenzamine before, at the time of testing and during the development of the reaction.[84]

Antihistaminic substances have been incorporated in ointment bases for local application in the treatment of allergic cutaneous disorders and also other skin conditions that are accompanied by pruritus. A 5 per cent ointment of either Benadryl or Pyribenzamine is too irritating for general usage. The ointments available now for local application on the skin are all of a concentration of 2 per cent. Perry[65] could not reduce the erythema associated with a histaminic wheal by the local application of a 2 per cent Benadryl ointment, and was also unable to relieve pruritus in patients with itching dermatosis by the local application of such an ointment. Sulzberger and co-workers[82] have observed that 2 per cent and 5 per cent Pyribenzamine ointments have consistent effectiveness only in the local treatment of lichen chronicus simplex and that such ointments are of diminutive value in the management of atopic dermatitis, contact dermatitis and pruritus vulvae and ani.

A 5 per cent aqueous solution of Pyribenzamine filters out erythemogenic wave lengths (2,800 to 3,100 Å) and when introduced into the skin by iontophoresis inhibits ultraviolet erythema. That such an effect is not due to the antihistaminic qualities of Pyribenzamine is indicated by the evidence that Benadryl, which has a different absorption spectrum, does not inhibit ultraviolet erythema, and that Pyribenzamine solution interposed between the light source and the skin but not on or in the skin filters out the erythemogenic rays.[43]

Migraine. There has been a remarkable paucity of reported observations on the effects of antihistaminics in the treatment of migraine.[17, 18, 9, 70, 13] The number of patients treated with various compounds, as reported to date, is so insignificant that no conclusions can be drawn.

Tuberculosis. It has been assumed that the inflammatory reaction that occurs in reinfection with tubercle bacilli or from a spread from the primary focus is partially due to the release of histamine. If this actually is the case, antihistaminic drugs might prevent tissue destruction by protecting sensitized cells from injury. Neohetramine, Pyribenzamine, Benadryl and Thephorin have been employed in doses of 150 to 400 mg. daily in the treatment of patients with pulmonary tuberculosis over a period of ten weeks to seven months.[41] Of six patients with acute exudative tuberculosis and two patients with acute tuberculous pneumonia, seven displayed x-ray evidence of clearing of the pulmonary lesion, decrease in the amount of sputum and reduction of cough. In six of the patients the first strength purified protein derivative (P.P.D.) Mantoux test reverted from positive to negative. Only four out of 14 patients with mixed exudative and productive tuberculosis showed evidence of improvement on x-ray films, but the first strength P.P.D. test became negative in 11 of the patients. Of eight patients with productive tuberculosis none showed any evidence of improvement but seven of the eight patients developed negative reaction to first strength P.P.D. Mantoux test. The most significant and hopeful observation of this interesting study was the disclosure that when three patients with acute exudative tuberculosis who were improving were taken off antihis-

ANTIHISTAMINE SUBSTANCES AND THE FORMS IN WHICH THEY ARE COMPOUNDED

Common Name	Made Available by	FORMS OF PREPARATIONS MADE AVAILABLE FOR									
		ORAL ADMINISTRATION					Parenteral Administration	LOCAL ADMINISTRATION			
		Tablets containing	Capsules containing	Expectorant containing	Elixir containing	Syrup containing	Vials - Sterile	Ointment	Nasal Solution	Ophthalmic	
										Solution	Ointment
Benadryl*	Parke-Davis & Company		a. 25 mg. b. 50 mg.	10.6 mg. per 4 cc. with 1.6 gr. NH_4Cl	10 mg. per 4 cc.		10 cc. 1 cc. contains 10 mg.	2% (water soluble base)			
Hydryllin (combination of diphenhydramine* and aminophyllin)	G. D. Searle & Company	25 mg. of diphenhydramine 100 mg. of aminophyllin			12.5 mg. of diphenhydramine and 50 mg. of aminophyllin per 4 cc.						
Decapryn	Wm. S. Merrell Company	a. 12.5 mg. b. 25 mg. (scored)				6.25 mg. per 5 cc.					
Pyribenzamine	Ciba Pharmaceutical Products, Inc.	a. 50 mg. (scored) b. 50 mg. (delayed action coating)		30 mg. per 4 cc. with 10 mg. of ephedrine and 80 mg. of NH_4Cl	30 mg. per 4 cc.			a. 2% (petrolatum base) b. 2% (water soluble base)	0.5%		
Histadyl†	Eli Lilly & Company	50 mg. (delayed action coating)	a. 25 mg. b. 50 mg. c. 100 mg. d. 25 mg. (with ephedrine, 8 mg.)			16 mg. per 4 cc.	10 cc. 1 cc. contains 20 mg.	2% (water soluble base)	0.5%		0.5%
Methapyrilene†	The Maltine Company	a. 50 mg. (with ephedrine 16 mg. and sodium pentobarbital 16 mg.) b. 50 mg. (with ephedrine 16 mg. and sodium pentobarbital 16 mg. delayed action coating)									

Thenylene†	Abbott Laboratories	a. 25 mg. b. 50 mg. c. 100 mg. d. 25 mg. (with ephedrine 8 mg.) ‡ e. 50 mg. (with ephedrine 24 mg.) ‡						2%‡			
Neohetramine	Wyeth, Inc.	a. 25 mg. b. 50 mg. c. 100 mg.				25 mg. per 4 cc.		2%‡			
Neoantergan	Merck & Company, Inc.	a. 25 mg. b. 50 mg.				10 mg. per 4 cc.‡	1 cc. contains 10 mg.‡	5%‡			
Antistine	Ciba Pharmaceutical Products, Inc.	100 mg.							0.5%	0.5%	
Thephorin	Hoffmann-LaRoche, Inc.	25 mg.				10 mg. per 4 cc.		5% (water soluble base)			
Trimeton	Schering Corporation	25 mg. (scored)			7.5 mg. per 4 cc.			3%			
Dramamine (8-chlorotheophyllinate salt of diphenhydramine*)	G. D. Searle & Company	100 mg. (scored)									
Tagathen	Lederle Laboratories, Inc.	25 mg.									
Pyrrolazote	The Upjohn Company	a. 25 mg. b. 50 mg.									
Diatrin	Wm. R. Warner Company	50 mg.									
Chlor-Trimeton	Schering Corporation	4 mg. (scored)									
Perazil	Burroughs Wellcome & Co.	50 mg. (scored)									

* Identical compounds.

† Identical compounds.

‡ Compounds to be made available but not marketed at time article submitted for publication.

taminic therapy, x-ray evidence of retrogression in the pulmonary lesion developed. Furthermore, reinstitution of antihistaminic substances reproduced subjective and objective improvement.

In regard to the use of antihistaminic drugs in the treatment of infections a note of caution is sounded from the results of recent studies by Halpern in France. The edema accompanying local infections in animals produced by staphylococcus and Salmonella typhimurium was inhibited by treatment with Phenergan. The very act of preventing local edema by antihistaminics might very well destroy a natural barrier to the diffusion of the infection, because 80 per cent of the infected animals treated with antihistaminics developed septicemia and visceral abscesses and eventually died, whereas the infected animals that were not treated with antihistaminics recovered.[34]

Motion sickness. During the course of time that the clinical effects of Dramamine (B-dimethylaminoethyl benzohydryl ether 8-chlorotheophyllinate) on patients with hay fever and urticaria were being studied in the allergy clinic at the Johns Hopkins Hospital, it was by chance observed that the drug dramatically relieved motion sickness. Subsequent studies by Gay and Carliner which[26] were conducted on a United States Army transport carrying soldiers from New York to Bremerhaven, Germany, authenticated without a doubt the efficacy of this substance in the treatment and prevention of sea sickness. Dramamine in doses of 100 mg. every five hours and before retiring prevented sea sickness in all but two of 134 men. Furthermore, the drug effectively relieved the manifestations of sea sickness within one hour after it was administered. Strickland and Hahn[81] reported that the drug is also efficacious in the prevention of air sickness.

Miscellaneous conditions. Benadryl,[72, 60] Pyribenzamine[66] and Thephorin[70] reduce the severity and the duration of subjective and objective symptoms brought on by exposure to cold in individuals hypersensitive to cold. Neoantergan[40] and Benadryl[40] are effective in the management of patients hypersensitive to liver extract. Hunter[40] has advocated 1 gm. of Neoantergan, in divided doses, 24 hours prior to the administration of liver extract. At times it is advisable to give 300 mg. just prior to the injection. Severe reactions to liver extract, however, are not modified by Neoantergan. Carryer[15] recommends desensitization with liver extract in addition to the oral administration of 50 mg. of Benadryl three to four times a day. As the intervals between liver injections are increased Benadryl is given only on the days of the liver injections. Local reactions to insulin may be combated by mixing insulin with an equal amount of a 1:1,000 Benadryl solution. However, that procedure may need to be supplemented by Benadryl given orally if the local reaction is severe or if urticaria is a part of the reaction.[47] Horton and Brennan[38] were able to abort attacks of trigeminal neuralgia with 100 mg. of Pyribenzamine given orally. Attacks of trigeminal neuralgia could be precipitated by the injection of 0.1 mg. of histamine and immediately relieved by either 100 mg. of Pyribenzamine or 100 mg. of Benadryl administered orally. Thirty mg. of Benadryl in 100 cc. of isotonic sodium chloride solution injected intravenously also alleviated the attacks. Bernstein and co-workers[8] reported Benadryl to be effective in the management of two patients with cardiac asthma and in five of ten patients with functional dysmenorrhea. Trimeton[13] is reported to have been of excellent benefit to one patient and of moderate benefit to another patient with radiation sickness. Pyribenzamine[66] does not inhibit the increase of gastric acidity induced by the administration of histamine.

SIDE-EFFECTS

There is a definite correlation between the incidence of side-reactions and the size of the dose of antihistaminic drugs, but there is no relationship between the kind of side-reaction that develops and the dosage. Furthermore, there is an individuality of response for each patient as far as different compounds are concerned, and this applies to therapeutic effectiveness as well as to side-effects. With few exceptions the quality of the side-reactions is similar for all compounds. The quantity of side-effects reported varies according to the drugs and also according to duration of time that they have been available for study. The customary and common side-effects, irrespective of compound, are: Drowsiness, dizziness, weakness and fatigue, nervousness, tremor, faintness, headache, apprehension, mental confusion, dryness of oral cavity, nausea, anorexia, abdominal pain, vomiting, blurring of vision, paresthesia, tachycardia, palpitation, and urinary frequency.[27, 8, 1, 38] The incidence of side-effects in patients treated with antihistaminic compounds varies from 10 per cent for some of the compounds to 50 per cent for others. Reactions are more liable to accompany the usage of Benadryl, Pyribenzamine, Hydryllin and Neoantergan[27, 8, 52, 89] than Antistine, Histadyl, Neohetramine and Thephorin.[17, 18, 27, 24, 7] Trimeton[13, 91] and Decapryn[14] are infrequently followed by side-effects, but to date insufficient data have been recorded on these compounds to permit comparison with the other members of antihistaminic family. Thephorin is unique among the various compounds in that insomnia and nervousness,[18, 11, 59, 62] and not drowsiness, are the most frequent unfavorable reactions.

The toxic reactions to Benadryl have been reviewed by Sachs[73] and the reader is referred to this article if reactions are encountered which are not enumerated in this treatise. It is necessary, however, to take cognizance of the ill-imagined allergic reactions to these compounds. Bronchial asthma has been exacerbated by Benadryl[86, 87, 20, 50, 10] and Pyribenzamine.[37] Eczematoid dermatitis from Pyribenzamine,[3, 19, 36] and contact dermatitis from Pyribenzamine ointment[82, 79] have been encountered.

It is interesting to speculate as to why antihistaminics should enhance at times such clinical manifestations of hypersensitivity as bronchial asthma.

Is such a reaction the result of the drying effect of these drugs; is it the result of a true hypersensitivity to the chemical compounds; or is it a manifestation of Pellerat's so-called "histaminoid accident," which this investigator claims to be due to the release of histamine from the cell receptors by the antihistaminics? The questions cannot be answered at this time, but certainly the matter is worthy of diligent study.

In selecting an antihistaminic drug for the treatment of an allergic disorder it is as imperative to consider carefully the percentage of incidence of side-effects as it is the percentage of good results obtained. If it is desirable to avoid drowsiness, Antistine, Histadyl, Thenylene, Thephorin, Neohetramine and possibly Decapryn and Trimeton should be prescribed. When a sedative effect is indicated, Benadryl, Hydryllin, Pyribenzamine and possibly Neoantergan take precedence. Optimal results can usually be obtained by using combinations of the various compounds and changing from one to the other as the case demands. It is indeed fortunate that a choice can be made from several preparations, and that the preparations are compounded in a variety of forms (see chart).

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